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IN THE UNITED STATES PATENT OFFICE

Application Serial No. 07/838,675 Our Ref: PT-1039

Filing Date: February 21, 1992

Applicants: DR. RUDOLF E. FALK
DR. SAMUEL S. ASCULAI

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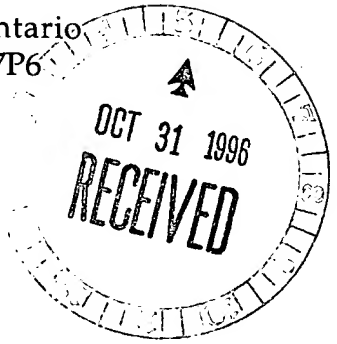

Title: TREATMENT OF DISEASE EMPLOYING HYALURONIC ACID AND NSAIDS

Inventors: RUDOLF E. FALK
SAMUEL S. ASCULAI

Examiner: DR. KATHLEEN FONDA

Group Art Unit: 1211 Due Date: July 16, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF SAMUEL SIMON ASCULAI
under §1.132

I, SAMUEL SIMON ASCULAI, make oath and say as follows:

1. I am the same Dr. Asculai who is one of the inventors of the subject matter of U.S. Patent Application Serial No. 07/675,908. This Application has now been

assigned to Hyal Pharmaceutical Corporation who continue to develop pharmaceutical products in accordance with the teachings of this Application.

2. I am the President and Chief Executive Officer at Hyal Pharmaceutical Corporation, the Assignee of this Application. I have a Ph.D. in Microbiology from Rutgers University. I have been involved in the pharmaceutical industry for in excess of thirty (30) years. Now shown to me and marked as **Exhibit A** to this my Declaration is a copy of my Curriculum Vitae.

3. With respect to this application, we have conducted tests using Formulation 3, also Formulation 2, and found the use of the formulation to be extremely successful with respect to basal cell carcinoma. Now shown to me and marked as **Exhibit B** to this my Declaration is a copy of the public announcement by the Assignee, Hyal Pharmaceutical Corporation, of the test results. Formulation CT 1101 is a formulation comprising 2.5% sodium hyaluronate and 3% diclofenac found as Formulation 3 in the application.

4. Additionally, we have conducted tests using dosage amounts taken from such formulation. Now shown and marked as **Exhibits C, D and E** are copies of clinical assessments and reports which have been prepared in respect thereto.

Exhibit C comprises test information, Study No. AK-CT1101-01 which relates to tests done in Australia using Applicant's Formulation 3 (2 $^{1}/_{2}$% HA, 3% diclofenac, molecular weight 661,000). Applicant herein had its Australian subsidiary and licensee carry out the tests and a public announcement was made in respect of those tests. **Exhibit C** comprises the press release and an excerpt from the Clinical Report.

Exhibit D comprises a second set of clinical studies that were conducted earlier under Study No. TDHA-AK-CDN-93-01. These studies were done in British Columbia on behalf of Hyal Pharmaceutical Corporation with the same formulation (Formulation 3 of this application). A copy of the press release and extract of the Clinical Studies forms **Exhibit D**. Both **Exhibits C and D** relate to the treatment of actinic keratoses (AK).

Exhibit E comprises a third set of test data related to the treatment of pain under Study No. AT-2101 0A 93-01 using Hyal AT-2101 with placebo gel for the treatment of breakthrough pain associated with osteoarthritis (OA) while on stable doses of NSAID therapy. This formulation is Formulation 3 of this application. The results are that dosage amounts containing 5 mg/cm^2 of hyaluronic acid applied to the skin are effective for treatment of actinic keratoses and dosage amounts containing 10 mg/cm^2 of the hyaluronic acid applied topically for treatment of pain is effective. Lesser amounts are also useful but not as effective.

5. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 15th day
of October, 1996.

SAMUEL SIMON ASCULAI

EXHIBIT A

SAMUEL S. ASCULAI

During the past 31 years, Sam Asculai has held various research, administrative and executive positions in the health care, chemical and biotechnology industries.

After a 10-year tenure with Ortho Pharmaceuticals, a division of Johnson and Johnson, where he was Director of the Microbiology Research Division, he joined Monsanto Company in St. Louis where he was responsible for the in-house biomedical research.

In 1981, he co-founded and ran Viral Genetics (later Exovir-NASDAQ), a company developing proprietary topical therapy for herpes infections.

In 1982, he joined ens BIO LOGICALS inc. to develop the drug now marketed by Syntex as Gancyclovir. He held a number of positions including Vice President Operations. In addition to his corporate responsibilities, he consulted for and managed a number of ventures in health care and agriculture biotechnology including International Genetic Sciences, FRM Agriculture Sciences, Syngene, Biotechnology General and FirstMiss Seed.

In 1988, he joined his colleague, Dr. R.E. Falk and formed Norpharmco Inc. to commercialize medical discoveries made at the Falk Oncology Centre. Norpharmco merged with Sterivet Laboratories Limited and since this event in 1990, Sam has been President and C.E.O. of the merged company, Hyal Pharmaceutical Corporation. He orchestrated Hyal's listing on NASDAQ and the IPO of its Australian subsidiary. Over the past six years he raised over $60 million Canadian in equity issues for Hyal and Hyal Australia.

Sam received a Masters and Doctorate degrees in Microbiology and Immunology from Rutgers University. He is author of a number of scientific papers and inventor or co-inventor of eight patents and fourteen current applications.

He was visiting scientist at the Weizmann Institute and Adjunct Professor of Biotechnology at the University of Missouri in St. Louis.

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EDUCATION:

Ph.D. 1972 Microbiology
M.S. 1970 Microbiology
Rutgers - The State University
B.S. 1965 Biology (Major), Chemistry (Minor)
Pace University

EMPLOYMENT:

1990 - Present	**Hyal Pharmaceutical Corporation**	
	President and Chief Executive Officer	
1988 - 1992	**Samuel Asculai Consultants**	
1988 - 1991	**FirstMiss Seed Company**	
	President and Chief Executive Officer	
1987 - Present	**First Mississippi Corporation/**	
	FRM Agricultural Sciences Partnership (FASP)	
	Director and FMC Representative	
1982 - 1988	**Enscor Inc./ens BIO LOGICALS INC.**	
1983 - 1988	Vice President	
1982 - 1983	General Manager - Joint Ventures	
1983 - 1985	**First Mississippi Corporation/International Genetic Sciences Partnership (IGSP)**	
1983 - 1985	Marketing Director	
1985 - 1986	President	
1981 - 1982	**Viral Genetics Ltd. (now Exovir)**	
	President and Scientific Director	
1975 - 1981	**Monsanto Company**	
1980 - 1981	Visiting Scientist - Dept. of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel	
1978 - 1981	Manager, R & D - Biomedical Technology	
1975 - 1978	R & D Manager	
1965 - 1975	**Ortho Pharmaceutical Corporation**	
1974	Acting Director - Division of Microbiology	
1974	Senior Scientist	

1972	Scientist - Division of Microbiology
1971	Associate Scientist - Division of Microbiology
1968	Assistant Scientist - Division of Microbiology
1965	Research Assistant - Division of Microbiology

Dr. Samuel S. Asculai, President and C.E.O. Dr. Asculai holds an M.S. and Ph.D. degree in Microbiology from Rutgers University. Dr. Asculai has been involved in the health care and biotechnology industries since 1965. From 1982 to 1988 he was Vice President of ens BIO LOGICALS inc. During 1981 he was President and Scientific Director of Viral Genetics Ltd. From 1975 to 1981 he was Manager of R&D Biomedical Technology in the Monsanto Company, St. Louis, Missouri and from 1965 to 1975 was employed by Ortho Pharmaceutical Corporation in New Jersey where he became Acting Director of the Division of Microbiology.

EXHIBIT B

AT THE COMPANY:

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FOR IMMEDIATE RELEASE
Mississauga, Ontario, Canada
September 21, 1993

PHASE III TRIALS POSITIVE FOR HYAL's TREATMENT FOR SKIN CANCER
HYAL-CT1101 SHOWS 87% RESPONSE RATE

Results from Hyal-sponsored Phase III clinical trials conducted at two independent centers for HYAL-CT1101, a topical treatment for basal cell carcinoma (BCC), were presented separately today by Dr. Kurt Gebauer (Fremantle, Western Australia) and Dr. Barry Lycka (Edmonton, Alberta) at the 5th World Congress on Cancers of the Skin in Berlin, Germany.

Dr. Gebauer evaluated a total of 90 patients in a randomized, double blinded, placebo controlled trial. Of the evaluable patients on active treatment for only eight weeks, 40% had complete or near complete resolution of their lesion and 47% had a partial resolution of their lesion, for a total of 87% positive responders. This was in contrast to 8% positive responders in the placebo group which was in line with published spontaneous remission rates. While 12% of patients on placebo experienced disease progression, no such disease progression was seen in the active treatment group. Statistical analysis using ANOVA shows an overwhelming significance $P<10^{-13}$ between the placebo and active groups.

Dr. Lycka presented results from his first 16 evaluable patients. All patients in the active group showed a positive response after only 8 weeks of treatment, with 33% of these being cured. No positive responses were observed in any of the patients in the placebo group.

Based upon these results, Hyal believes that HYAL-CT1101 offers the first non-invasive, non-toxic, non-scarring therapy for the treatment and management of basal cell carcinoma, a locally malignant skin tumour that is the most frequent cancer in the caucasian population. In North America more than 500,000 new cases are reported each year. In Australia, public interest is great as

the annual incidence there approaches 1 per 100 people, the highest incidence rate in the world.

The Company intends to use these results as a basis for submissions to health regulatory agencies for obtaining product market approvals.

Hyal specializes in the development and world wide commercialization of pharmaceutical formulations utilizing its proprietary Hyaluronic Acid based drug delivery technology. Hyal is currently conducting Phase III clinical trials at 20 independent centres in Canada, the U.S.A., Australia and a number of European countries for its three lead products: HYAL-CT1101 for the treatment of basal cell carcinoma and actinic keratosis, HYAL-AT2101 for the topical treatment of pain and HYAL-AV2201 for the intravenous treatment of moderate to severe pain.

Hyal Pharmaceutical Corporation's shares are traded on the Toronto Stock Exchange under the trading symbol HPC and on NASDAQ National Market System under the trading symbol HYALF.

EXHIBIT C

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CONTACT:
Barbara Kay, Manager Investor Relations

NEWS RELEASE

HYAL PHARMACEUTICAL AUSTRALIA LIMITED (HPAL) RELEASES POSITIVE CLINICAL TRIAL RESULTS

MISSISSAUGA, Ontario, Canada – November 28, 1995 – Hyal Pharmaceutical Corporation (TSE: HPC, NASDAQ: HYALF) announced today that pursuant to the requirements of the Australian stock exchange (ASX), its Australian subsidiary, HPAL, released clinical-trial results on Hyal's gel for the topical treatment of Actinic Keratosis. Actinic Keratoses (AKs, solar keratosis or "sun spots") are common, pre-cancerous skin lesions caused by over-exposure to sunlight.

One hundred and fifty patients were treated at three centers for up to three months. The patients received either active drug or placebo and were evaluated during and after the treatment period.

Of the 150 patients originally enrolled in the trial, 87 were evaluated 30 days after the completion of therapy. In this group, 64% of patients receiving the active drug had a greater than 50% reduction in the number of AK lesions. This compared to 29% of patients receiving placebo. The difference between the active drug group and the placebo group at the thirty day follow-up was statistically significant ($p=0.002$).

While this trial evaluated lower dosages than are currently being used in ongoing , North American studies, the cure rate (patients with no visible or palpable AK lesions) was statistically significant for the active drug group versus placebo ($p=0.002$).

Hyal specializes in the development and worldwide commercialization of pharmaceutical formulations utilizing its proprietary drug delivery system, Hyaluronan Induced Targeting (HIT)™ Technology.

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CLINICAL REPORT
for the clinical study entitled

A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY TO ASSESS THE SAFETY AND EFFICACY OF CT1101 IN THE TREATMENT OF ACTINIC KERATOSES

STUDY NUMBER : AK-CT1101-01

Conducted by:

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Hyal Study Coordinators:

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Maria Ginzler, BA (Hons). MSc. RN

Report Statistician:

Kate Downs BSc. MApp Stats
IDT Biomedicus
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St Leonards NSW 2065

Report Author:

Mike Vanzieleghem, BSc.

1. SUMMARY

This was a randomised, double blind, controlled multicentre trial comparing Hyal's CT1101 (3% diclofenac in 2.5% hyaluronan topical gel) to the gel vehicle (placebo) in the treatment of actinic keratosis. Patients were selected who presented with lesions on the head and neck area, the hands, or the arms. The study included a baseline visit at which time inclusion/exclusion criteria were evaluated including a physical examination, medical history, lesion assessment, and haematologic and clinical chemistry assessments. Patients were excluded if they had a sensitivity to non steroidal anti inflammatory drugs (NSAIDs), had a significant concurrent illness, were taking systemic corticosteroids, antineoplastic drugs, etretinate, isotretinoin and/or vitamin A, had a skin condition which could confound the study, recently received another investigational drug, or worked outdoors or deliberately exposed their skin to sun or UV light. Patient clinic visits were held at weeks 4, 8, and 12 with a post termination follow up at approximately 30 days post week 12 visit. At these visits, lesion sites were assessed by lesion counts and/or categorical lesion assessments, adverse events were reviewed, and investigational drug use was accounted for. Upon cessation of therapy, haematology and clinical chemistry were repeated and the details of termination were recorded.

The gel was to be applied in a dose of 0.25 grams twice daily on a targeted area of skin of approximately 5 cm. by 5 cm. for up to 12 weeks. Treatment was stopped if complete resolution of lesions occurred. Mean compliance was very high with slightly more than the recommended dose being applied (0.68 grams per day or 136% of recommended).

One hundred and fifty (150) patients were included in this investigation; 73 allocated to active gel treatment (49 male:24 female) and 77 (40 males:37 females) to placebo. Mean age was 68 (10 SD) years in the active group and 69 (11 SD) years in the placebo group. The location of the lesions were head and neck 45:46, hands 23:25, and arms 5:6, for active:placebo treatment groups. Lesion severity was scored at baseline as mild, moderate or severe; mild were 27 and 16, moderate were 36 and 45, and severe were 10 and 16, active and placebo patients, respectively.

Fifty (50) of 73 patients (68%) completed the full 12 weeks of drug administration in the active group compared to 66 of 77 (86%) in the placebo treated group. Withdrawals were due to adverse events in 16 active and 3 placebo treated patients. Other reasons included non-attendance (1 active patient:2 placebo patients), protocol violations (3:3), patient request (1:2), or targeted lesions completely resolved (3:3).

Mean baseline lesion counts were well balanced by treatment with 9.8 (6.6) in the active group and 11.2 (7.7 SD) in placebo patients. There was considerable disparity between investigators' sites; site 1 had higher baseline counts (14.6 [7.0 SD] and 17.0 [7.9 SD] active:placebo) than site 2 (6.8 [3.0 SD] and 6.9 [3.6 SD]) and site 3 (4.4 [2.0 SD] and 7.9 [5.2 SD]).

Initially, the primary efficacy parameter was to be end of treatment lesion counts assuming that all effects to be demonstrated by the topical treatment would be accrued by that time (12 weeks). However, like several other actinic keratoses preparations, a more optimal response was identified as occurring at least 30 days after treatment cessation, as evidenced in a previously completed open study at the University of British Columbia in Canada.

The primary analysis in this present investigation therefore also includes a post termination follow up lesion count. Fewer patients participated in the post termination follow up as the

visit was added after the study had been initiated (n=45 active; n=42 placebo) but prior to clean file.

Mean lesion count reductions assessed by univariate tests were not significantly different between treatments at end of treatment (5.5 [7.3 SD] active versus 4.7 [6.9 SD] placebo; p=0.293 Wilcoxon Rank Sum, p=1.0 Bonferroni adjusted) or expressed as percent differences (42.5% versus 29.5%; p=0.047 Wilcoxon, p=0.714 adjusted). Multivariate testing of delta baseline lesion counts using a Generalised Linear Model included the statistically significant factors (I) investigational site (p=0.0001 for site 1 with greater lesion reductions than sites 2 and 3), (II) baseline lesion area (p=0.0299 with arms having smaller lesion reductions than hands or head/neck), and (III) compliance (p=0.0001 with greater quantity of gel resulting in greater reductions in lesion counts) in the final GLIM model which supported the univariate findings.

Mean lesion counts at post termination follow up were highly significant for treatment contrasts by Wilcoxon test (p=0.0009) and adjusted (p=0.023) with a mean decrease by active treatment of 6.2 [7.5 SD] lesions (56.1% reduction) compared to 2.4 [4.3 SD] lesions (23.6% reduction) by placebo. This was true for both data presented as actual counts and expressed as percent change. The multivariate test supported this claim taking into account the only significant confounding factor at post termination follow up (investigational site effect at p=0.0001). The multivariate treatment contrast was significant at p=0.0398.

Treatment contrasts for the number of patients with zero lesion counts (complete lesion resolution) by end of treatment (21 active:10 placebo) and by post termination follow up (17 active:4 placebo) were both statistically significant (p=0.029 and p=0.002, respectively). The mean time to complete resolution of lesions was 72 (25 SD) and 78 (22 SD) days in the active and placebo treatment groups, respectively (ns).

The frequency of patients with 50% or greater lesion count reductions were 39 active treated (53%) and 32 placebo treated (42%) at end of treatment (ns). By the post termination follow up visit, that contrast became significant (p=0.002) with 29 patients in the active group (64%) and 12 in the placebo group (29%).

Of the patients who experienced complete resolution of their lesions before or by the end of treatment (21 active and 10 placebo), 9 patients in the active treated group (43%) had a new lesion appear before the study was terminated compared to 7 (70%) in the placebo group. The time to appearance of a new lesion was 93 (34 SD) days for active and 62 (30 SD) days for placebo treatments, respectively.

Adverse events were coded according to COSTART. There was a total of 81 events in 30 patients in the active group and 31 events for 18 patients in the placebo treatment (p=0.03). The most common single events were rash, pruritus and dry skin in 29%, 22% and 22% of active treated patients and in 9%, 8%, and 3% of placebo treated subjects. Rated as severe in intensity were 15% of all the active group's events listed under the COSTART body system "Skin and Appendages" compared to 23% of similar placebo events, regardless of causality. There were 5 non study drug related adverse events rated as serious.

The topical treatments exhibited no untoward effects on either the haematological or clinical chemistry variables tested.

These data support that the active gel's efficacy is best evaluated after the topical treatment has been stopped for at least 3 weeks and a dermal immunologic response can be optimised.

The placebo effect was likely jointly contributed to by natural lesion regression, moisturising effects of the hyaluronan gel, and/or an actual therapeutic benefit of the vehicle itself. Regardless of the relative contribution of each of these factors, the overall placebo effect was quicker to wane in that new lesion appearance was reported sooner and more frequently in the gel vehicle treated patients.

Hyal's CT1101 topical diclofenac gel for the treatment of actinic keratoses exerts significant therapeutic effects in the dose, and for the duration of exposure, investigated. The active gel was associated with greater reductions in lesion counts than the placebo gel vehicle. However, the response rate was somewhat lower in this study than that demonstrated in the open study at the University of British Columbia where approximately 80% of patients experienced complete response to slightly higher doses of gel (0.5 grams per dose). From this it can be concluded that future studies should ensure the optimisation of CT1101's effects by investigating the higher dose (0.5 grams b.i.d.) in controlled clinical studies and/or possibly by exploring more frequent daily dosing.

In summary, these present data support that CT1101 is a potentially viable agent for the treatment of actinic keratoses.

EXHIBIT D

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FOR IMMEDIATE RELEASE
October 17, 1994
Mississauga, Ontario, Canada

HYAL-CT1101 CURES 85% OF PATIENTS WITH ACTINIC KERATOSIS

Hyal Pharmaceutical Corporation ("HYAL") (TSE: HPC and NASDAQ NMS: HYALF) announced today exciting preliminary results in the treatment of actinic keratosis. The results presented at the European Academy of Dermatology's Skin Therapy Update '94 are from the trial conducted at the University of British Columbia in which 85% of patients who used HYAL-CT1101 were cured, while the remaining 15% showed marked improvement. A "cure" was defined as the absence of all visible and palpable lesions and "marked improvement" included patients with substantially all of their lesions resolved.

Actinic keratoses or solar keratoses are precancerous lesions occurring on sun damaged areas of the skin, primarily on the face, scalp and upper extremities. Individual lesions are pink and scaly on the surface of the skin but dermatologists, by touching the skin, can detect underlying lesions as palpable lumps. If left untreated, up to 10% of lesions are reported to progress to squamous cell carcinoma. The trial was designed to assess the effectiveness of HYAL-CT1101 in treating not only the visible but also the underlying lesions.

David Harper, Vice President Development and C.O.O., stated, "The high degree of therapeutic value demonstrated by HYAL-CT1101 in this study leads us to believe that it will prove to be a very attractive alternative to all conventional forms of therapy, particularly in light of the significant side effects and limited efficacy of the currently approved treatments. Phase III double-blind placebo controlled trials are ongoing in Australia and will start soon in North America."

HYAL specializes in the development and worldwide commercialization of pharmaceutical formulations utilizing its proprietary Hyaluronan Induced Targeting (HIT) Technology™. HYAL is currently conducting Phase III clinical trials at independent centres in Canada, the U.S.A., Australia and a number of European countries for its three lead products: HYAL-CT1101 for the treatment of basal cell carcinoma and actinic keratosis, HYAL-AT2101 (HYANALGESE™-D) for the topical treatment of pain and HYAL-AV2201 for the intravenous treatment of moderate to severe pain.

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CLINICAL REPORT
for the clinical study entitled

AN OPEN STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOPICAL 3% DICLOFENAC IN 2.5% HYALURONIC ACID GEL (HYAL ST5101) IN THE TREATMENT OF ACTINIC KERATOSES

STUDY NUMBER : TDHA-AK-CDN-93-01

by: Dr. David McLean, M.D.,F.R.C.P.(C.) and Dr. Jason Rivers, M.D.,F.R.C.P.(C.)
University of British Columbia
Division of Dermatology
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Clinical Research Associate and Director, Clinical Services, Hyal

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REPORT AUTHORS: Michael Vanzieleghem, B.Sc.
and
Jason Rivers, M.D.,

1 SUMMARY

An open label study of the efficacy and safety of topical 3% diclofenac and 2.5% hyaluronan gel was performed in 30 patients suffering from actinic keratosis. Hyal's topical agent comes in the form of a clear gel which was applied in a dose of 1 gram b.i.d.. The study duration was up to 180 days unless lesions were cleared before that time upon which treatment was stopped. After cessation of therapy, a follow up visit was performed at 30 days. The measures recorded included treatment response on a 7 point scale (ranging from "cure" to "much worse"), assessment of efficacy and tolerability on a 4 point scale ("poor" to "excellent"), and a lesion count. Interim visits occurred at days 60, 120, and 180 days plus the 30 days follow up. Other therapies which could interfere with the outcome measures were not allowed. Haematologic and biochemistry parameters were evaluated before treatment and after and adverse events were recorded in standardized fashion.

One patient was lost to follow up prior to returning for any assessments and was therefore lost to the analysis. The net result of the study was that 29 patients took 50% of the expected dose of diclofenac gel over 84 days which resulted in a "cure" rate of 81% at the 30 day follow up or last available assessment. The only clinically relevant adverse effects seen were those related to dermal irritation (typically rash [33%], eczema [23%], and pruritus [20%]). Study treatment was discontinued in **11** patients due to these events. However, of these patients, all but two were complete treatment responses after 30 days of treatment discontinuation. The two exceptions were scored as marked improvements. There were no effects of either treatment on clinical chemistry or haematologic parameters.

A simple test (Use Test) to re-challenge volunteer patients who had experienced eczematous reactions to the gel during the study proper was performed after that study was completed. Five (5) patients and 5 healthy volunteers were exposed to up to 1 gram of diclofenac gel twice daily on their upper inner arm, a site distal to the original target area for actinic keratosis treatment, for 7 days. Sera were taken and tested for anti-diclofenac antibodies after 7 days of treatment exposure. No evidence of the presence of such antibodies were apparent in any samples tested. Transient erythema with no related systemic effects was evident in only one patient.

The 3% diclofenac/2.5% hyaluronan gel effected complete remission of actinic keratotic lesions in over 80% of patients with a limited level of discomfort due to dermal adverse events. The medication caused no deleterious systemic effects. Hyal's topical gel appears to be a high probability candidate for continued study under more rigorous trial conditions.

Amended page, November 6, 1995
see bold underline

CLINICAL REPORT
for the clinical study entitled

AN OPEN STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOPICAL 3% DICLOFENAC IN 2.5% HYALURONIC ACID GEL (HYAL ST5101) IN THE TREATMENT OF ACTINIC KERATOSES

STUDY NUMBER : TDHA-AK-CDN-93-01

by: Dr. David McLean, M.D.,F.R.C.P.(C.) and Dr. Jason Rivers, M.D..F.R.C.P.(C.)
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REPORT AUTHORS: Michael Vanzieleghem, B.Sc.
and
Jason Rivers, M.D.,

1 SUMMARY

An open label study of the efficacy and safety of topical 3% diclofenac and 2.5% hyaluronan gel was performed in 30 patients suffering from actinic keratosis. Hyal's topical agent comes in the form of a clear gel which was applied in a dose of 1 gram b.i.d.. The study duration was up to 180 days unless lesions were cleared before that time upon which treatment was stopped. After cessation of therapy, a follow up visit was performed at 30 days. The measures recorded included treatment response on a 7 point scale (ranging from "cure" to "much worse"), assessment of efficacy and tolerability on a 4 point scale ("poor" to "excellent"), and a lesion count. Interim visits occurred at days 60, 120, and 180 days plus the 30 days follow up. Other therapies which could interfere with the outcome measures were not allowed. Haematologic and biochemistry parameters were evaluated before treatment and after and adverse events were recorded in standardized fashion.

One patient was lost to follow up prior to returning for any assessments and was therefore lost to the analysis. The net result of the study was that 29 patients took 50% of the expected dose of diclofenac gel over 84 days which resulted in a "cure" rate of 81% at the 30 day follow up or last available assessment. The only clinically relevant adverse effects seen were those related to dermal irritation (typically rash [33%], eczema [23%], and pruritus [20%]). Study treatment was discontinued in **11** patients due to these events. However, of these patients, all but two were complete treatment responses after 30 days of treatment discontinuation. The two exceptions were scored as marked improvements. There were no effects of either treatment on clinical chemistry or haematologic parameters.

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Amended page, November 6, 1995
see bold underline

4.3 THERAPY

4.3.1 STUDY DRUGS

The study drug was 3 % diclofenac in a 2.5 % HA based gel. The lot number used was ULD2 with shelf life to 12/95. An additional 10 patients were added to the study after November 1, 1994. The active gel lot number was also ULD2 with shelf life to 12/95. The drug was supplied in 50 gm aluminum lined tubes. Packaging was done at Hyal Pharmaceutical Corporation's technical office at 3909 Nashua Drive, unit 5, Mississauga, Ontario, Canada L4V 1R3 by the QC staff. A controlled drug packaging process was followed by Hyal's QC department and a drug reconciliation was performed by the Clinical Monitor upon completion of the study.

Drug packaging included labeling each tube with identification to the study number, tube number, the sponsor's name, the investigator's name, the drug's expiry date and lot number, the patient's randomized study number, and a space for the patient's initials. A warning was added that the treatment was to be administered by a qualified investigator only and storage conditions were specified. The treatment tubes were packaged with a pre-marked dispenser that fit onto the 50 gram tube mouth and which was used to measure out the desired amount of gel.

The principal investigator assumed responsibility for securing and controlling distribution and use of the investigational medications. It was discussed that upon completion of the study that all used and unused medication containers were to be returned to Hyal for reconciliation.

4.3.2 TREATMENT PLAN

The study required that 1 gram of Hyal ST-5101 (30 mg of diclofenac sodium) would be administered to the target lesion(s) twice each day throughout the study period. The volume of gel was measured using a vaginal applicator which fit tightly onto the end of the 50 gm tubes and which was clearly marked for easy measurement of a 1 gram dose by the Hyal QC department. The gel was applied to the skin over the lesion and rubbed in. There was no provision for continuation of the investigational treatment upon completion of the study. The PUT amendment to the protocol required that the gel be applied to the left upper inner arm in a dose of 1 gram twice daily for 7 days to investigate dermal sensitization.

4.3.3 COMPLIANCE

The tubes of investigational treatments were weighed prior to being returned to Hyal after the study. The weight of the tubes was known prior to being shipped and therefore an evaluation of compliance with expected dosing was possible. This method did not enable that specific details of the timing of missed doses be described but it was intended to be a general method to both reflect basic patient behaviour.

follow up), #102 experienced an adverse event requiring cessation of therapy (eczema), and #116 was cured prior to the 30 day follow up visit.

5.3A PROTOCOL VIOLATIONS

There were three patients who violated in the strictest sense the requirements of the protocol. They are listed in Table 4. Both patient #s102 and 109 had basal cell carcinoma lesions removed. Exclusion criteria number 7 stated that patients would be excluded from the study if they had any skin conditions which could confound the results of the study specifically basal and /or squamous cell carcinoma. However the meaning of the criteria was to relate the dermal cancers to the specific site of the treatment. Neither of the cases included the same specific site of treatment for actinic keratoses and are therefore not truly significant confounders of the treatment outcome. Patient #108 violated exclusion criteria number 4 which stated that no NSAID was to be taken during the study. This patient did so for an unrelated reason but in doing so violated the protocol. The relevance of this co-administration of ibuprofen to the study outcome for this patient is uncertain. As the study is an open evaluation of the gels performance and in view of the fact that no rigorous statistics are being performed in this small population, these subjects were handled as evaluable in the most general intent to treat approach.

5.4A COMPLIANCE

Compliance was measured by the weighing of tubes after the study was completed as a general index of how well the patients were following the required dosing instructions. The procedure was satisfactory to provide quantitative evidence of compliance in each patient after the study was completed. Patient diary cards were a back up source of compliance information (Appendix E Volume II).

The patients were instructed at the start of the study that 1 gram doses of investigational gel were to be applied to the affected skin 2 times daily throughout the study for a total daily dose of 2 grams. Mean compliance was 1.0 (0.7 SD) grams per day with a range of 0.1 to 2.2 grams (Table 5). This amounts to a mean of 50.0 % (36.2 SD) of expected use in the 24 patients for whom complete data were available. (Appendix A2 Volume II). The distribution of patients above and below 50 % compliance was well balanced (10 and 14, respectively).

5.5A DURATION AND AMOUNT OF INVESTIGATIONAL TREATMENT EXPOSURE

The study was a medium term investigation of up to 180 days of treatment exposure plus the 30 day follow up at doses as previously discussed. Compliance to the timing of specific study visits was variable as it was not required that those with treatment success or adverse events would continue the treatment. These individuals were encouraged to return to the clinic when those events occurred and cease medications and return 30 days later for follow up. The patients were included in the study for an average of 118 (46 SD) days with a median of 97 days (Table 6). This data is based on all 29 patients who participated in the treatment portion of the study (excludes patient # 115) and includes the 30 day follow up (Appendix A1 Volume II).

5.9A CONCOMITANT MEDICATIONS

Medications taken during the study are listed in Appendix E Volume II. Few incidents of other medications being used were reported. Only the case of patient #108 who self administered ibuprofen for another condition was worthy of note.

5.10A EFFICACY

5.10.1A GLOBAL ASSESSMENT OF LESION RESPONSE

The physician derived global efficacy evaluations of lesion response were considered "primary" outcomes. These data were derived using a 7 point interval scale. The statistical analyses address the mean difference between treatment and a "0" score meaning there was no change in the lesion to treatment. This contrast was performed for both the visual assessment and the photographic assessment (Table 11). It was evaluated at both the end of treatment ie at the discontinuation visit and at the follow up visit at 30 days post treatment cessation.

At the discontinuation visit there was a very highly significant increase in the score ($p=0.0001$) compared to a no effect score for both visual and photographics assessments. The mean value in both cases was 2.4 meaning the effect was somewhere between a moderate to marked improvement. This analysis included all 29 patients who received treatment and returned for at least one visit. After 30 days post treatment, the follow up visit demonstrated a more dramatic effect with the mean of both visual and photographic assessments of 3.7. This mean score is interpretable as near to complete "cure" across all patients . This information is described as frequency data in Table 12. Upon evaluation at the **drug discontinuation visit** the majority of patients are "cured" (48% and 45% on visual and photographic assessments respectively). At the **follow up visit** the response was remarkably higher with 81% "cure" rate on visual and photographic assessment respectively. An additional 15% of patients had a "marked improvement" and only one patient experienced "no change" to topical diclofenac treatment. (Appendix C1 and E Volume II).

5.10.2A NUMBER OF LESIONS

The lesion count (Table 13) provided evidence of the reduction in lesion numbers over time. Baseline mean lesion count was 2.7 (4.5 SD) in the ten last patients entering the open primary study. The Table shows a decrease in mean lesion number at the discontinuation visit but at a value somewhat higher than would be expected based upon the interval scores for lesion response. The mean change from baseline at the drug discontinuation visit is, in fact, positive entirely due to the fact that patient #125 experienced an increase in numbers of lesions at the 60 day visit when adverse events were encountered and the drug was discontinued. The patient's final outcome was "cured". In general, the mean number of lesions (n=8) at follow up supports the beneficial treatment effects described elsewhere with a mean lesion count of 0.9 (1.7 SD) and a mean decrease in lesion count from baseline of 2.1 (2. SD) (Appendix C2 and E Volume II).

6 DISCUSSION

The data can be summarized in a few simple statements. The administration of Hyal's 3% diclofenac/2.5% hyaluronan gel resulted in very high response rates upon study completion and which were associated with a degree of dermal adverse events. The drug gel complex clearly passed through the skin into the epidermis as intended to a considerable extent to cause these very highly significant effects. Compliance was quite low in this study but that did not seem to adversely effect outcome. The dermal events were both clinically and immunologically considered to be irritant in nature and not "allergic", at least with respect to diclofenac itself. The level of severity of the dermal adverse events presented were felt to be considerably less than that which might be seen with a competitive treatment, 5-FU. No evidence of systemic side effects typically associated with diclofenac were demonstrated in this population. Each of these important issues will be touched upon in this discussion before conclusions are drawn.

It appears intuitive that the large molecule of hyaluronan must not pass through the stratum corneum and into the epidermis due to its very large dimensions (about 500,000 daltons). However that is apparently incorrect as has been demonstrated experimentally by Franz cell results using tagged hyaluronan[12] and drug in human breast tissue and as is now apparently demonstrated in this clinical investigation. Relevant to the bio mechanics of such a feat are the permeability coefficient of the drug vehicle complex across the stratum corneum which is related to the chemical properties of both, and the molecular size of the complex. Enhanced partitioning into deeper tissues with penetration enhancers is followed by uptake by the microcirculation in the typical dermal drug application scenario. The success of the dermal circulation in carrying off such molecular "interlopers" is very dependent on size alone[14], at least from an aqueous vehicle. This may in part explain why dermal penetration of the active agent is remarkably low after topical application of the hyaluronan gel. Once in the epidermis, movement into the microcirculation is very inefficient due to hyaluronan's very high molecular weight and diclofenac's association to some degree with the polysaccharide. This lack of systemic circulation of diclofenac after topical application of Hyal's gel has been previously referred to [11] and hence the paucity of adverse events normally associated with diclofenac when administered *per os*. It is less easy at this time to explain the mechanism by which the hyaluronan molecule makes its way across the stratum corneum but that work continues at the time of writing. Based upon this present work, the drug apparently does get into the epidermis and has a residence time adequate to perform its pharmacologic activity. It is not known how the diclofenac molecule exerts its effects on actinic keratotic lesions at this time.

The quantity of drug necessary to elicit the pharmacologic response is uncertain but it is very evident that about 0.5 grams b.i.d. is sufficient as that is approximately what was administered in this study. The reasons for the low compliance numbers was uncertain although it was stated by the investigator that the patients felt, in their opinion, that the 1.0 gram application was a large quantity for a single dose and that it was seen as difficult to rub into the sometimes small targeted area requiring treatment. The study results suggest that in fact 0.5 grams is probably better from both the perspective of the successful outcome of such treatment and the acceptability from the patients' perspective. Compliance was actually less of an issue in the PUT where it was at its lowest at about 25% or 0.25 grams per dose on average. The nature of that study was to re-elicit an allergic dermatitic response if an allergic reaction had been established during the prinicipal treatment study. It was felt that low compliance would not adversely affect that objective as, if such a situation were latent, it would be expected to present even with the

Table 5. Average amount of study gel used and percent of compliance

Variable	Mean (SD)	Minimum - Maximum	Number of patients
Average amount of study gel used [g/day]	1.0 (0.7)	0.1 - 2.2	24[b]
Percent of compliance[a]	50.0 (36.2)	5.1 - 108.5	24[b]

Percent of compliance	Number (percent) of patients
Less than 50%	14 (58)
At least 50%	10 (42)

[a] Percent of compliance = 100% * (grams of gel used per day / expected study gel use).
Expected study gel use was 2 g/day (1 g bid).
[b] Total amount of study gel used was missing for patients #101, #102, #104, #115, #120 and #124.

Table 13. Number of lesions at treated site (subset of patients)[a]

Visit	Mean (SD)	Minimum - Maximum	Number of patients	Mean (SD) change from baseline
Baseline	3.1 (2.6)	1 - 7	10[a]	-
Drug discontinuation	2.7 (4.5)	0 - 12	7[b]	0.3 (2.6)
Follow-up	0.9 (1.7)	0 - 5	8[c]	-2.1 (2.5)

[a] Patients #121 to #130
[b] Missing information for patients #123, #126 and #128.
[c] Missing information for patients ##124 and #125.

EXHIBIT E

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NEWS RELEASE

CLINICAL COMPARISON DEMONSTRATES HYANALGESE-D HAS THE EDGE OVER VOLTAREN EMULGEL IN RELIEVING ARTHRITIS PAIN

MISSISSAUGA, Ontario – December 13, 1995 – Hyal Pharmaceutical Corporation (NASDAQ/NNM: HYALF; TSE: HPC) announced today results of a Phase III clinical comparison of its Hyanalgese-D with the widely marketed product, Voltaren Emulgel. Hyanalgese-D, a topical gel, has been developed to alleviate the pain of arthritis experienced by countless millions of people worldwide. Diclofenac is the active pain-relief ingredient in both products.

The results were presented at the Seventh International Seminar on the Treatment of Rheumatic Diseases held in Tel Aviv, Israel by the well known European rheumatologist, Dr. Karl Chlud of Vienna, Austria.

Dr. Chlud reported that, "Hyanalgese-D demonstrated significantly better efficacy over Voltaren Emulgel in the following parameters: pain at rest; pain during movement and tenderness of the affected joint. Overall effectiveness in providing pain relief, assessed by both patients and investigators, significantly favored the Hyanalgese-D product."

This Hyal-sponsored Phase III clinical trial followed 112 patients at centres in Germany, Austria and the Czech Republic. Under the double-blind, cross-over clinical design, separate patient groups suffering from osteoarthritis or rheumatoid arthritis of the knee, ankle or shoulder, applied either Hyanalgese-D or Voltaren Emulgel four times a day for four consecutive days. Patients were evaluated three times during the first hour after first application and again after the first application on day four of treatment. All patients then stopped treatment for seven days. When treatment resumed, patients previously treated with Hyanalgese-D were given Voltaren Emulgel, while those treated with Voltaren Emulgel received Hyanalgese-D. Again, treatment and clinical evaluations were conducted exactly as in the first four day period.

Hyal specializes in the development and worldwide commercialization of pharmaceutical formulations utilizing its proprietary drug delivery system, Hyaluronan Induced Targeting (HIT) Technology™.

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CLINICAL REPORT
for the clinical study entitled

A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PARALLEL DESIGNED CLINICAL STUDY TO COMPARE THE SAFETY AND EFFICACY OF HYAL AT-2101 WITH PLACEBO GEL IN THE TREATMENT OF BREAKTHROUGH PAIN ASSOCIATED WITH OSTEOARTHRITIS (OA) WHILE ON STABLE DOSES OF NSAID THERAPY

STUDY NUMBER : AT-2101 OA 93-01

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1 SUMMARY

This investigation was conducted as a randomized, double bind, parallel group study comparing the efficacy and safety of active 3% diclofenac topical gel in a 2.5% hyaluronan base against the hyaluronan based gel vehicle containing no active diclofenac (placebo). Male and female subjects were selected if they demonstrated a history of osteoarthritis (OA) of the knee, hip, spine, foot, hand, or shoulder of at least 1 year duration supported by X-ray confirmation. Subjects had to be taking a stable dose of oral NSAIDs for at least 1 month prior to study start which they maintained throughout the investigation. Subjects were excluded if they had any condition or history which could adversely affect their health if they were to participate or would confound the study outcomes. Additional analgesics other than the subjects' maintenance dose of oral NSAID were contraindicated during the study.

The study was of 2 weeks duration. The entry/baseline visit included a review of all inclusion/exclusion criteria, a medical history and physical examination, and a review of concurrent therapies. The subject provided informed consent prior to initiation of the study. Baseline scores for pain, OA activity, joint swelling, joint tenderness, and a defined activity score (test of functional capacity related to pain) were made on a five point scale (1=none, 2=mild, 3=moderate, 4=severe, and 5=very severe) by the subject and the physician. The primary outcome measure was OA pain as assessed by the subject. Adverse events were recorded along with any intercurrent illnesses that the subjects' experienced during the study. Pain was measured over the first 4 hours of the study, every 15 minutes over the first hour and every hour over the next 4 hours.

Visits occurred at days 7 and 14. Examinations of the effects measures were repeated at these visits. The subjects were instructed to keep a diary card of their pain scores every day prior to and 1 hour after dosing. A physical examination was repeated upon completion of the study.

One hundred and nineteen (119) subjects were enrolled, 59 to the active treatment and 60 to the placebo treatment. The mean average age, weight, and height of the population were 67 (9 SD) years, 169 (42 SD) pounds, and 65 (4 SD) inches, respectively. Blood pressure and heart rate were normal overall and the medical and physical examinations revealed no unusual findings. Most importantly, the treatment groups were well matched by demographics and history. The mean duration of diagnosed OA was 10.2 (9.2 SD) and 10.3 (10.2 SD) years for the active and placebo groups, respectively.

One subject was withdrawn due to violation of study entry criteria (active group). Thereafter there were 6 withdrawals from the study; 4 in the placebo group due to dermal adverse events and 2 in the active group (adverse event and unsatisfactory therapeutic response). The average use of investigational gel treatment was 8.3 (1.1 SD) and 8.1 (1.0 SD) grams per day, representing compliance of 104% and 102% for active and placebo treatments, respectively.

The distribution of joints or anatomical areas being studied was as follows: spines 41%, hands 24%, knees 23%, feet 7%, shoulders 3%, and hips 2%. Subjects were classified using the ARA functional classification scheme and were distributed relatively equally between the treatment groups (10, 47, and 2 subjects versus 12, 45, and 1 for Class I, II, and III, active and placebo, respectively).

The predominant class of NSAID drugs being used concurrently during the study was the propionic acid derivatives (38 subjects) followed by nabumetone (28 subjects) and the salicylates (19 subjects). The remainder received arylacanoic acids, etodolac, oxicams, indomethacin and sulindac, tolmetin, and acetaminophen.

Analysis of the primary efficacy variable, subject assessed pain as recorded in the case report form, provided evidence that the active diclofenac gel treatment caused a greater analgesic effect than the placebo gel (p=0.057). Analyses of daily diary recordings of subject assessed pain scored 1 hour prior to each of the 4 daily doses and meaned for each of those doses over both week 1 and week 2 generally supported this adjunctive analgesic effect (p=0.021 to p=0.231, maximum to minimum treatment differences). Secondary endpoints were more relevant to anti inflammatory effects such as change in OA disease activity and change in joint swelling. It was known that the chronic oral NSAID therapy would provide significant anti inflammatory effects beyond which it was unlikely the adjunctive anti inflammatory effects of topical treatment could be demonstrated. Not surprisingly, none of the secondary endpoints demonstrated treatment differences. Neither did active diclofenac treatment provide evidence of superiority over placebo during the first dose interval.

Adverse events were primarily isolated to dermal effects at the site of investigational drug application. These included pruritus in 12% and 25% and rash in 8% and 18% of active and placebo treated subjects, respectively. The subjects' reported the active topical diclofenac gel as better tolerated than the placebo gel vehicle (p=0.039). There were no clinically significant effects of either treatment on blood chemistry or haematology.

In summary, the results of this study support that active diclofenac gel, in the dose tested, is clinically effective as an adjunctive analgesic therapy in treating exacerbations of OA in subjects maintaining stable doses of oral NSAID. While dermal events were clinically relevant, they were less prevalent in the active treatment group and did not result in any systemic expression.

3. OBJECTIVE

The study objective was to evaluate the efficacy and safety of topically applied 3 % diclofenac in 2.5 % HA gel (Hyal AT-2101) in comparison with placebo in those subjects who experience osteoarthritic breakthrough pain while on a stable dose of oral NSAID therapy.

4 SUBJECTS AND METHODS

4.1 OVERALL STUDY DESIGN

This was a randomized, double-blind, placebo-controlled, parallel group study. Subjects who met the inclusion and exclusion criteria within 1 week of an exacerbation of OA pain were randomly assigned to topical treatment with either Hyal AT2101 (diclofenac gel) or placebo gel. Before randomization, the investigator identified a single joint which was targeted for treatment in each subject. Subjects were required to apply the study gel 4 times daily for the duration of the treatment period of 2 weeks. Study evaluations were made at weeks 1 and 2 after randomization. Table 1 lists the schedule of events. The placebo control group was necessary as there is currently no topical treatment for pain associated with OA approved for use in Canada or the United States with which to make comparison. To prove superiority over placebo was therefore the primary objective of the study. The duration of the study was set at 2 weeks as this time frame is clinically relevant to pharmacologically controlling a "flare" of OA. Only one anatomical area was treated.

4.3 THERAPY

4.3.1 STUDY DRUGS

The study drug was 3 % diclofenac in a 2.5 % HA based gel, lot number ULD2 with shelf life to December 1995. The drug was supplied in 50 gm aluminum lined tubes. Identical placebo gel, that is identical vehicle not containing the active diclofenac, was packaged in identical 50 gm tubes as the control, Lot number UEE1 with shelf life to May 1995. Drug packaging was performed under controlled conditions at Hyal Pharmaceutical Corporation's technical office at 3909 Nashua Drive, Unit 5, Mississauga, Ontario, Canada L4V 1R3 by the QC staff. Three tubes were provided for each subject. A drug reconciliation was performed by the CRM (HRA, New Jersey) upon completion of the study.

Drug packaging included labelling each tube with identification of the study number, the sponsor's name, the active drug's expiry date, the patient's randomized study number, both active and placebo lot #'s, and a space for the subject's initials. A warning was added that the treatment was to be administered by a qualified investigator only and storage conditions were specified. The labels were three-part. The above information was included both on the portion affixed to the tube itself and to the second portion which was not attached to the tube and which was meant to be detached by the investigator's staff for attachment in a drug reconciliation record. The third portion of the label was a blinded (pre-sealed), detachable label which contained information re: the identity of the subject's study medications. This was intended to be opened only in the event of a medical emergency which would require that this information be known right away.

The principal investigator assumed responsibility for securing and controlling distribution and use of the investigational medications. It was discussed that upon completion of the study that all used and unused medication containers were to be returned to Hyal for reconciliation.

4.3.2 TREATMENT PLAN

The study required that 2 grams of Hyal AT2101 (60 mg of diclofenac sodium) or placebo gel would be applied 4 times per day for 2 weeks. Two (2) grams of gel was administered using a pre-marked vaginal applicator which fit tightly on the end of the 50 gm treatment tubes and which provided for simple measurement of a 2 gram dose. Instructions on the actual application of the gel were kept quite simple and no reference was made to the degree to which subjects were to rub the gel into the affected area. There was no provision for continuation of the investigational treatment upon completion of the study.

4.3.3 COMPLIANCE

The tubes of investigational treatments were weighed at the investigational site after their return to the clinic. The weight of the tubes was known prior to their being shipped. Therefore an evaluation of compliance to recommended dosing was possible.

5.4 COMPLIANCE

Compliance was evaluated by weighing the investigational drug tubes at the time they were dispensed and upon their return to the clinic. It was intended to be a general index of how well the subjects were following the required dosing instructions. The procedure was satisfactory to provide quantitative evidence of compliance in each subject after the study was completed. This data was then used to identify a sub-group of subjects for analysis of the primary efficacy endpoint of the study based on a relevant level of adherence to the dosing instructions.

The subjects were instructed at the start of the study that 2 gram doses of investigational gel were to be applied to the affected joint 4 times daily throughout the study for a total daily dose of 8 grams. Mean compliance including both active and placebo gel treated subjects was 8.2 (1.0 SD) grams per day with a range of 5.0 to 11.0 grams (Table 3.2). This amounts to a mean of 103% (12.6 SD) of expected use in the 119 subjects (Table 3.3). Compliance was similar in the 2 treatment groups (8.3 [1.1 SD] versus 8.1 [1.0 SD] active and placebo groups respectively). (Volume II Sections K, L, and W- data listings; Volume III Appendix A2 - statistics)

Table 3.2 STUDY MANAGEMENT: *Average amount of study gel applied [g/day]*

Summary Statistics	Active Group	Placebo Group	Combined
Mean	8.3	8.1	8.2
SD	1.1	1.0	1.0
Maximum	10	11	11
75% quartile	9	9	9
Median	8	8	8
25% quartile	8	8	8
Minimum	5	5	5
Number of patients	59	60	119

Table 3.3 STUDY MANAGEMENT: *Percent of expected study gel use*

Summary Statistics	Active Group	Placebo Group	Combined
Mean	104.3	101.8	103.0
SD	13.1	12.1	12.6
Maximum	130	132	132
75% quartile	111	109	111
Median	105	102	103
25% quartile	99	94	96
Minimum	69	59	59
Number of patients	59	60	119

Expected study gel use was 8 g/day.